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EXAMINER
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BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

**MAILED**

Application Number: 09/835273  
Filing Date: 04/13/2001  
Appellant(s): LADINE ET AL

**FEB 27 2007**

**GROUP 1600**

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Charles B. Katz  
For Appellant

**EXAMINER'S ANSWER**

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Zenhausern et al. US 20020094531; priority date 06/14/1999

Demirev et al. Analytical Chemistry, 1997, 69(15), 2893-2900

Zeng et al. Analytical Chemistry, 1998, 70(20), 4380-4388.

Henry et al. Analytical Chemistry News & Features: Focus, April 1, 1999, p.  
264A-268A

Cotter et al. Journal of Mass Spectrometry, 34, 1368-1372, 1999

Orient et al. Review of Scientific Instruments, Volume 68,3, pp. 1393-1397, 1997.

#### **(9) Grounds of Rejection**

The following grounds of rejection are applicable to the appealed claims.

**A.** Claims 1,2,5-18, 22-45 are rejected under 35 U.S.C. 103(a) as obvious over Zenhausern in view of Demirev et al. or Zeng et al.

The instant claims are directed to method of parallel analyzing of multiple protein samples. The parallel processing is carried out using a parallel array of mass spectrometry systems. The protein samples are obtained by sampling a biological system at multiple time intervals, and submitting each sample to separation technique to obtain multiple protein samples for analysis by mass spectrometry. The mass spectrometry analysis provides data indicating identity and abundance of one or more proteins.

**Zenhausern** teaches a method for monitoring information in a medium, the medium comprising at least one biomolecule, the method comprising screening the medium with a screening means comprising a n number of sensing probes, where n is an integer of at least one so that more than one physical, chemical, or physico-chemical change (claim 1). The n number of sensing probes is an array of mass-spectrometers

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(claims 3,9, paragraph [0047]). The biomolecules are, for example, proteins ([0027]). The reference teaches analyzing plurality of biomolecules (“at least one biomolecule”, see, e.g., claim 1) using plurality of sensing probes (“the  $n$  number of sensing probes can be at least one mass spectrometer” – see paragraph [0047]). The method of Zenhausern can be used, for example, to analyze the results of protein degradation, e.g., by multiple cycles of Edman degradation, i.e., to analyze multiple multicomponent samples at multiple time intervals. See paragraphs [0068], [0070]. Monitoring a biomolecule includes interrogating the medium by coupling a sensor responsive to any changes of the medium or biomolecule, and includes direct detection and monitoring of biomolecular reactions in real-time (see Abstract and claims 1,13,14). In particular, changes in concentration of the biomolecule are detected (claim 13). The results are subjected to multivariant analysis (claims 20,21, paragraph 0012)).

Zenhausern does not specifically teach preparing sample as instantly claimed, namely submitting each of samples to a separation technique. However, such difference would appear to be minor and *prima facie* obvious to one skilled in the art, as it would be obvious to one skilled in the art to use separation techniques to prepare protein samples before mass-spectrometry identification. See, for example Demirev et al reference, which describes multiple separation of components before mass-spectrometry identification. In addition, note that Zenhausern reference itself teaches that chromatography system (e.g., gas chromatography, liquid chromatography, or

capillary electrophoresis) can be added in conjunction with an appropriate sensor technique (e.g., mass spectrometer) – see paragraph [0077].

As for the need to analyze multiple, rather than single samples, use of MS spectrometry to analyze multiple samples is, again, well known in the art. See, for example, Zeng et al demonstrating analysis of multiple multicomponent protein samples using parallel mass spectrometry (albeit on a single MS) to analyze parallel arrays of protein libraries.

With respect to claims 6,7, the reference is silent about the exact amount of components, but it would be within the purview of skill in the art to select the amount of compounds of interest.

With respect to claims 12,17,18,36, selection of methods of preparing samples and selecting appropriate time intervals of sampling would be obvious to an artisan as a part of routine optimization of result-oriented parameters.

With respect to claims 14-16,22,43,44, it would be obvious to an artisan that measurement of a time course of changes in biological system can be made in response to exposure of the biological system to a stimulus.

Therefore it would be obvious to apply parallel mass spectrometry described in Zenhausern to any problem requiring multiple measurements of samples containing plurality of components, such as, for example, measurement of plurality of proteins from a quiescent or stimulated biological sample.

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**B.** Claims 1,2,5-18, 22-45 are rejected under 35 U.S.C. 103(a) as obvious over Chang et al., and Demirev et al., and Chalmers et al., and Zeng et al. in view of Zenhausern, and further in view of Henry et al, Cotter et al., and Orient et al.

The instant claims are directed to method of parallel analyzing of multiple protein samples. The parallel processing is carried out using a parallel array of mass spectrometry systems. The protein samples are obtained by sampling a biological system at multiple time intervals, and submitting each sample to separation technique to obtain multiple protein samples for analysis by mass spectrometry. The mass spectrometry analysis provides data indicating identity and abundance of one or more proteins.

There is well recognized need in the art to analyze complex multi-component protein mixtures with a combination of separation and analytical techniques, chromatography and mass spectrometry. Thus, **Demirev et al** explore feasibility of a "massively parallel" mass spectrometry of proteins and suggests that practical implementations of parallel mass spectrometry seem feasible for protein libraries containing from several hundreds to several thousand individual components, or for monitoring the diversity of up to a thousand reaction products. See p. 2900, last two paragraphs. In their theoretical analysis, Demirev et al assume multiple separation of components, but intentionally do not dwell into practical details of mass spectrometry arrangement (p. 2898, right column, 1<sup>st</sup> full paragraph) and mention that there is a

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number of instrumental factors that must be accounted for in practical implementation of “parallel” mass spectrometric approach, such as e.g., detection efficiency and accuracy of mass spectrometry.

**Chalmers et al.** and **Zeng et al.**, are other exemplary references describing chromatography/mass-spectrometry systems for analysis of complex peptide mixtures and proteome. Thus, **Palmer** teaches that proteome analyses can be concerned with profiling and comparisons of multiple constituents, and that in profiling and comparative work, the need for multiple analyses emphasizes the importance of achieving high-throughput, and that advantages of miniaturized systems for the purposes of improved analyte detection and enhanced sample throughput are widely recognized (p. 385, 1<sup>st</sup> full paragraph). **Zeng et al.** teaches parallel MS analysis of different samples, albeit on a single mass-spectrometer (see abstract).

The primary references, although describing plurality of parallel separation units, do not teach multiple system of parallel mass-spectrometers that analyze the separated protein samples – in these references multiple samples are analyzed by the same mass-spectrometer, or a duet of mass-spectrometers analyzing various aspects of the same sample.

This is understandable as an artisan would be aware of prohibitively high cost of mass-spectrometry system. However, the idea of combining of several analytical devices is well known in the art.



For example, Zenhausern reference addressed in the preceding rejection, teaches a multisensor array comprising a number of sensing probes, in particular, such as mass-spectrometers.

Further, with regard to technical problems operating multiple mass-spectrometers (cost, size, weight), a new generation of simplified small and light-weight mass-spectrometers have been designed recently. As example of references teaching such simplified, small, and light-weight mass-spectrometers, the references of **Henry et al**, **Cotter et al.** , and **Orient et al.** are cited.

Therefore, it would be *prima facie* obvious to analyze multiple protein samples using multiple mass-spectrometers instead of a single mass-spectrometers, because prior art teaches processing of multiple samples using an array of equivalent devices, such as mass spectrometers (Zenhausern), and also teaches availability of simplified mass spectrometers better suited for combining into such multiple analyzing arrays. One would expect that analyzing multiple samples using a set of analytical devices (i.e., mass spectrometers) would be at least as effective as using a single analytical device.

With regard to the dependent claims, if there are any differences from the prior art, these differences appear to be minor, as addressed in the preceding rejection.

**(10) Response to Argument**

**A.** Rejection of claims 1,2,5-18,22-45 under 35 U.S.C. 103(a) as obvious over Zenhausern in view of Demirev et al or Zeng et al.

Applicant argues that Zenhausern does not teach that its multisensor array can be used to conduct parallel analysis of different samples. First, to clarify, the claim language addresses samples as "multiple", not "different", even though this distinction is not critical for the discussion. Second, Zenhausern addresses analysis of multiple samples as it is directed to "monitoring and/or discriminating between biomolecules during a reaction process" (paragraph [0001]). The whole concept of Zenhausern is a versatile multisensor system to measure plurality of biomolecular characteristics, and nowhere the reference is limited to the measurements of the components of single sample. Even if it were limited to the measurements of the components of single sample, it is Examiner's position that it would be obvious that a system comprised of multiple sensors such as mass-spectrometers, can be equally configured for measuring multiple characteristics of the same sample, or a characteristic(s) of multiple samples. Thus, for example, Example 1 of Zenhausern illustrates measuring plurality of products (time change in accumulation of various PCR products) by plurality of detectors. Furthermore, as for the need to analyze multiple, rather than single samples, use of MS spectrometry to analyze multiple samples is well known in the art. See, for example, Zeng et al demonstrating use of parallel mass spectrometry - albeit on a single MS - to analyze parallel arrays of protein libraries.

Examiner agrees that Zenhausern does not teach preliminary separation of a sample before subjecting protein samples to mass-spectrometry. However, this distinction is addressed in the obviousness part of rejection discussing that it would be obvious to use separation techniques to prepare protein samples before mass-spectrometry identification.

**B.** Rejection of claims 1,2,5-18, 22-45 under 35 U.S.C. 103(a) as being obvious over Demirev et al., and Chalmers et al., and Zeng et al., in view of Zenhausern, and further in view of Henry et al, Cotter et al., and Orient et al.

Applicant acknowledges (p. 7, last full paragraph) that the general concept of combining several analytical devices may be well known in the art. Applicant then argues that none of the prior art describe “architecture and workflow” of the present invention. However, there is no claim language addressing “architecture and workflow”, and these terms are not being linked to particular claim limitations.

Examiner appreciates that Appellant recognizes that a rationale for combining references can be implied or reasoned from the prior art. In the instant case, the need for “massively parallel” mass spectrometric monitoring of diversity of protein samples – either resulting from a time-dependent changes of a biological system, or being members of protein library – is well known in the art; see Demirev or Zeng references, for example. Until certain stage of development of technology, the use of plurality of mass-spectrometers was limited by prohibitively high cost of mass-spectrometry equipment. For example, Zeng reference while describing parallel mass-spectrometry

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measurements of multiple samples, uses a single MS system. However, the need for achieving high-throughput analysis resulted in development of simplified and small mass-spectrometers (as exemplified by references of Henry et al, Cotter et al., and Orient et al.). In addition, Zenhausern describes use of parallel arrays of sensors, such as mass-spectrometers, to analyze time-dependent changes in components of biological systems (e.g., proteins). Taken together, the claimed method of analyzing multiple protein samples using parallel array of mass spectrometry systems is obvious.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.


Respectfully submitted,

Michael Borin  
Primary Examiner



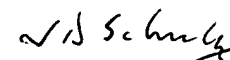
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